Filaggrin Genotyping and Skin Disease

Filaggrin is a major component of the cornified cell envelope, an essential skin layer that acts as a water barrier and inhibits the entry of microbes, allergens and irritants.[1] Loss-of-function mutations in the filaggrin gene (FLG) reduce the expression of the filaggrin protein in the skin, and have been strongly associated with the following diseases:

- Atopic dermatitis (AD), a chronic inflammatory skin disease associated with cutaneous hyperreactivity to environmental triggers, affects up to 30% of children and 10% of adults in the US, with about 600,000 new cases a year. The effect of FLG on AD risk is higher than that of any other confirmed candidate gene for atopic diseases.[2]
- Ichthyosis vulgaris (IV), an inherited skin disorder that is characterized by dry scaly skin. The prevalence of IV in the US is 1 in 250 people. It is well recognized in clinical practice that atopic dermatitis and ichthyosis vulgaris often co-exist.[3,4]
- Asthma, a chronic inflammatory disorder affects about 22 million people in the US, of which 6 million are children (NHLBI). FLG mutations are strongly associated with eczema-associated asthma and may therefore identify AD patients who are prone to developing asthma.[2]

Clinical Utility

- In infants with atopic dermatitis and food sensitization FLG may predict asthma before the onset of symptoms and predict exacerbations [8]
- Early clinical intervention and enhanced clinical management of atopic dermatitis patients at risk for moderate-to-severe disease
- Relatives of atopic dermatitis patients can be screened for FLG mutations to facilitate genetic risk prediction for other family members
- Genetic diagnosis of Ichthyosis vulgaris
- Increased risk for allergic sensitization in patients with FLG mutations [9]

Ethnic Differences in Filaggrin Gene Variants

Two common FLG variants (R501X and 2282del4) with an estimated combined allele frequency of approximately 6%, as well as 18 less common variants, all in trans with R501X and 2282del4, have been identified in individuals of European descent. The combined mutation frequency of R501X, 2282del4, 3702delG, R2447X and S3247X mutations is 9% in the European population.[3]

In Asian populations (Chinese, Japanese, Korean and Taiwanese), R501X is the only member of the European variant group that has been replicated.[5]

In African-American individuals, the only European-associated variant that has been reported is R501X. It occurs at a frequency of 3.2%.[6]

Clinical Significance of Filaggrin Mutations

A meta-analysis[2], combining twenty-four studies on FLG mutations and eczema involving 5,791 cases, and 1,951 families, as well as seventeen studies on asthma involving 3,138 cases, and 1,511 children concludes the following associations with FLG mutations:

- Strong increase in AD risk (Odds ratio: 3.12; 95% CI, 2.57-3.79)
- Association with severe and dermatologist diagnosed AD (Odds ratio: 4.24; 95% CI, 3.09-5.81)
- Significant association with asthma (Odds ratio: 1.48; 95% CI, 1.32-1.66)

Test Information

Test Name:	Filaggrin Genetic Test
Description:	Detection of the five most frequent FLG mutations from European populations: R501X, 2282del4, R2447X, S3247 and 3702delG.
Test Code:	FLG
Test Method:	Real Time PCR
Sample Type:	**Buccal swab*:** Puritan cat. no. 25-1506 1PF **OR** **Blood:** One full ACD soln A vacutainer or full ACD soln B vacutainer or a minimum or 500 μL whole blood aliquot from ACD-anticoagulated blood. A full EDTA vacutainer is also acceptable. **Note:** Samples with less than specified amounts will be rejected.
Normal Range:	By report
Turn Around Time:	9 days
CPT Codes:	83891, 83898x5, 83896x10, 83912

* Please refer to test menu at NJlabs.org for detailed collection instructions

Related Tests

DISEASE	TEST NAME [TEST CODE]	SAMPLE TYPE	TAT	TRANSPORT
Skin Infections	Superficial wound culture and sensitivity [varies**]	Varies**	Varies**	Varies**
Allergic Disorders	Total IgE [IGE]	0.25 mL serum is required for one allergen. Collect in SST or plain red top tube	48 hrs	Ambient, refrigerated or frozen
Allergic Disorders	Specific IgE-foods, inhalants, microbial antigens [varies**]	0.25 mL serum is required for one allergen. Collect in SST or plain red top tube	48 hrs	Ambient, refrigerated or frozen

** Please refer to test menu at NJlabs.org

References:

1. Presland RB, Coulombe PA, Eckert RL, Mao-Qiang M, Feingold KR, Elias PM, J Invest Dermatol 2004; 123:603–606.
2. Rodrıguez E, Baurecht H, Herberich E, Wagenpfeil S, Brown SJ, Cordell HJ, Irvine AD, and Weidinger S, J Allergy Clin Immunol 2009;123:1361-70.
3. Brown JS and McLean WHI, J Invest Dermatol 2009; 129:543–552.
4. Smith FJ, Irvine AD, Terron-Kwiatkowski A, Sandilands A, Campbell LE, Zhao Y et al. Nat Genet 2006; 38:337–42.
5. Akiyama A. British Journal of Dermatology 2010; 162:472–477.
6. Gao P, Rafaels NM, Hand T, Murray T, Boguniewicz M, Hata T, Schneider L, Hanifin JM, Gallo RL, Gao L , Beaty TH, Beck LA, Barnes KC, Leung DYM. J Allergy Clin Immunol 2009; 124:507-13.
7. Marenholz I, Kerscher T, Bauerfeind A, Esparza-Gordillo J, Nickel R, Keil T, Lau S, Rohde K, Wahn U, Lee Ya. J Allergy Clin Immunol 2009; 123: 911-6
8. Basu K, Palmer CNA, Lipworth BJ, Irwin McLean WH, Terron-Kwiatkowski A , Zhao Y, Liao H, Smith FJD, Mitra A, Mukhopadhyay S. Allergy 2008; 63:1211–1217.
9. Weidinger S, Illig T, Baurecht HJ, Irvine AD, Rodriguez E, Lacava AD, Klopp N,Wagenpfeil S, ZhaoY, Liao H, Lee SP, Palmer CNA, Jenneck C, Maintz L, Hagemann T, Behrendt H, Ring J, Nothen MN, McLean WHI, and Novak N. J Allergy Clin Immunol 2006;118:214-9.